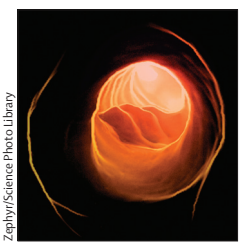
Metformin for cardiovascular disease: promise still unproven



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Published Online
November 7, 2013
http://dx.doi.org/10.1016/S2213-8587(13)70171-2

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The role of metformin in cardiovascular disease is under investigation. Aside from its established use for patients with type 2 diabetes, metformin is thought to be beneficial for cardiovascular disease, although solid evidence is lacking. The alleged protective effects of metformin in cardiovascular disease seem at least partly unrelated to its effects on glucose metabolism. The investigators of the Carotid Atherosclerosis: MEtformin for insulin ResistAnce (CAMERA) study[1] investigated the effect of metformin on carotid intima-media thickness (cIMT) in a double-blind randomised controlled trial of 173 patients with proven coronary heart disease, but without diabetes. After 18 months, cIMT progression did not differ significantly between metformin and placebo groups (slope difference 0·007 mm per year, 95% CI –0·006 to 0·020; p=0·29) The investigators did report a reduction in HbA_{1c} or insulin concentrations in patients assigned to metformin compared with those assigned to placebo.

Patients in the study had coronary heart disease and were therefore treated according to current guidelines, with all patients taking statins. Thus, the window of opportunity for improving atherosclerosis as measured by cIMT was small. The study was powered to detect a difference in cIMT between the metformin and control groups of 0·021 mm after 18 months. This difference was partly based on the study of Meaney and colleagues[2] in which 40 patients with features of metabolic syndrome were either treated with metformin or received no additional treatment. After 12 months, patients in the metformin group had a greater reduction of cIMT than in the control group (–0·1 mm, p=0·04 *vs* –0·02 mm, p=not significant). By contrast with patients in CAMERA, patients in the study by Meaney and colleagues[2] had higher baseline LDL-cholesterol, and data for use of statins were not presented, so the potential for cIMT reduction was probably greater. Katakami and colleagues[3] also studied the effect of metformin on cIMT. They assessed 118 patients with type 2 diabetes treated with glibenclamide over 3 years. Addition of metformin was associated with less progression of cIMT compared with placebo (0·003 mm *vs* 0·064 mm; p<0·0001). However, few patients (n=29) were taking statins. The studies by Meaney and colleagues and Katakami and colleagues show that metformin might reduce progression of cIMT in the absence of statin treatment. The CAMERA study shows that the effect of metformin—in addition to current best treatment, including statins—on cIMT is probably small or negligible. In two upcoming trials, the Copenhagen Insulin and Metformin Therapy trial (CIMT; NCT00657943) and the REducing with MetfOrmin Vascular Adverse Lesions in type 1 diabetes trial (REMOVAL; NCT01483560), the effect of metformin on cIMT will be assessed in 500 patients with type 1 diabetes and 950 patients with type 2 diabetes in whom statin use will be monitored, respectively.[4] We are interested to see whether these studies will show a beneficial effect of metformin in addition to statins.

Proof-of-principle trials such as CAMERA are usually powered to assess markers thought to be reliable proxies for outcomes. Ideally, a strong causal relation exists between the surrogate endpoint and outcome. cIMT is an established marker for the diagnosis of atherosclerotic disease, and a surrogate approved by the US Food and Drug Administration. Conversely, little evidence exists of a direct association between improvement of cIMT and outcome. Moreover, the experimental evidence for a direct effect of metformin on cIMT is weak.[5] Experimental evidence of an effect on myocardial function is more established: several studies show that metformin is associated with a reduced size of myocardial infarct.[6] Furthermore, metformin exerts anti-thrombotic effects, which could explain the improved outcome in atherothrombotic disease.[7] Likewise, in a non-ischaemic experimental study of rats, metformin prevented heart failure and improved myocardial function, suggesting that metformin might even improve myocardial function irrespective of ischaemia.[8] In several retrospective analyses[9,10] of patients with diabetes with concomitant coronary artery disease and even heart failure, use of metformin was associated with improved survival independent of glycaemic control. Ongoing randomised, double-blind clinical trials such as the Metformin in CABG trial (MetCAB; NCT01438723) and the Glycometabolic Intervention as Adjunct to Primary Percutaneous Intervention in ST Elevation Myocardial Infarction Trial (GIPS-III; NCT01217307) will elucidate whether metformin can reduce myocardial infarct size, improve

resilience to ischaemia, and improve left ventricular function after ischaemia-reperfusion injury. Like cIMT, the effect of metformin on myocardial function and infarct size is also a surrogate endpoint for clinical outcome.

Whether the primary endpoint of CAMERA or secondary endpoints such as HbA_{1c} best represent cardiovascular outcome is unclear. The definitive evidence for the role of metformin in non-diabetic cardiovascular disease will have to be provided by large randomised clinical trials powered for cardiovascular outcomes such as the Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT; ISRCTN34875079), in which 12 000 patients with high cardiovascular risk and dysglycaemia but without diabetes, will be assigned to metformin or placebo for 5 years. Until then, the role of metformin for improving cardiovascular outcomes has promise, but is still largely unproven.

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The importance of incretin therapies for managing type 2 diabetes

A quarter of a century after the discovery of incretin hormones and their impaired regulation of insulin and glucagon secretion in type 2 diabetes,[1] specific treatments to improve the diminished incretin effect have become widely available for glycaemic control in type 2 diabetes. Incretin treatments consist of either oral DPP-4 inhibitors, which decrease the clearance of secreted incretins GLP-1 and GIP, or injectable analogues of GLP-1. Relative freedom from hypoglycaemia, an absence of weight gain, and additivity in glucose control in combination with metformin have largely driven the increasing acceptance of these drugs.[2,3]

Despite the proliferation of many new drugs for diabetes management, low persistence and adherence of patients to these drugs remain key drivers of residual hyperglycaemia in this population. Increasing complexity of therapeutic interventions is one key reason for low adherence.[4] For this reason, the use of combination treatments for managing type 2 diabetes is increasingly common, since reducing the number of tablets per day by combining two agents into a single tablet reduces complexity of treatment for the patient.[3] Because the once daily DPP-4 inhibitors can be used in combination with long-acting metformin preparations, this combination effectively reduces the pill burden for many patients, especially those with early, asymptomatic type 2 diabetes, in which many patients believe their therapies to be somewhat optional.

Another strategy to increase adherence and persistence is to reduce the frequency of medication administration. Thus, once-daily medications seem preferable to those that must be administered twice or three-times daily. Recently, once weekly drugs have begun to make an appearance in the

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Published **Online**
November 1, 2013
http://dx.doi.org/10.1016/S2213-8587(13)70157-8

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